Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

RESEARCH CORRESPONDENCE

ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection

Furong Liu,[*,‡] Xin Long,[*,‡] Bixiang Zhang,[*,‡] Wanguang Zhang,[*,‡] Xiaoping Chen,[*,‡] and Zhanguo Zhang[*,‡]

*Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; ‡Hubei Province for the Clinical Medicine Research Center of Hepatic Surgery, Wuhan, Hubei, China

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus that causes coronavirus disease 2019 (COVID-19) in human beings, has caused a serious public health issue.[1] Attention to pancreatic injury is lacking, which may impact patients' prognosis. In this study, we explored the expression and distribution of angiotensin-converting enzyme 2 (ACE2), the receptor of SARS-CoV-2, in the pancreas. Combined with clinical data, we showed that pancreatic injury can occur in some COVID-19 patients.

Methods

A public database was used to explore the expression and distribution of ACE2 in normal pancreases. We also retrospectively analyzed patients diagnosed with COVID-19 from January 1, 2020, to February 15, 2020, in Wuhan Tongji Hospital and Wuhan Jin Yin-tan Hospital. We collected hospital admission data, laboratory tests, and imaging tests from clinical electronic medical records. Severe COVID-19 was defined when patients had 1 of the following criteria: (1) shortness of breath and respiratory frequency $\geq$30/min; (2) finger pulse oximeter oxygen saturation at rest of 93% or less; or (3) oxygenation index of 300 mm Hg or less. More details about clinical data and public data set analysis are described in the Supplementary Methods.

Results

In the GTEx database (https://gtexportal.org), we found that the messenger RNA level of ACE2 was higher in the pancreas than in the lung (Figure 1*A*) ($P < .001$, Wilcoxon signed-rank test). To investigate the distribution of ACE2 in the pancreas, we analyzed 2 single-cell RNA sequencing data sets. After identifying different types of pancreatic cells (Figure 1*B* and *D*), we found that ACE2 was expressed in both the exocrine glands and islets (Figure 1*C* and *E*). The details are listed in Supplementary Table 1.

Furthermore, we analyzed pancreatic injury after SARS-CoV-2 infection. Our study cohort included 121 COVID-19 patients (46 women, 75 men), with a median age of 57 years (interquartile range, 43–72 y). In mild cases, 1.85% (1 of 54) had increased levels of both amylase and lipase. In patients with severe COVID-19, 17.91% (12 of 64) and 16.41% (11 of 64) had increased amylase and lipase levels, respectively (Table 1). On computed tomography scan, 5 patients with severe COVID-19 (7.46%) showed changes in the pancreas, mainly focal enlargement of the pancreas or dilatation of the pancreatic duct, without acute necrosis. Of the 13 patients with pancreatic injury, 3 severe patients showed increased amylase and lipase levels on admission. In addition, 2 patients had a history of nonsteroidal anti-inflammatory drug use, and 4 patients had been treated with glucocorticoids during hospitalization, which may be associated with drug-induced pancreatitis[2] (Supplementary Table 2). Three patients had suspected symptoms of pancreatitis such as abdominal pain or vomiting. Of note, the clinical symptoms could not be recorded among severe patients requiring mechanical ventilation under sedation. Meanwhile, 5 critically ill patients with pancreatic injury died and 8 were discharged. These clinical data show that pancreatic injury can occur in some COVID-19 patients, mainly in those with severe illness.

Discussion

In this study, we focused on the expression of ACE2 in the pancreas and the damage to the pancreas in a proportion of patients with SARS-CoV-2 infection. We found that ACE2 was expressed in the pancreas of normal people, and this expression was slightly higher in the pancreas than in the lungs, indicating that SARS-CoV-2 also might bind to ACE2 in the pancreas and cause

Abbreviations used in this paper: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2020.04.040

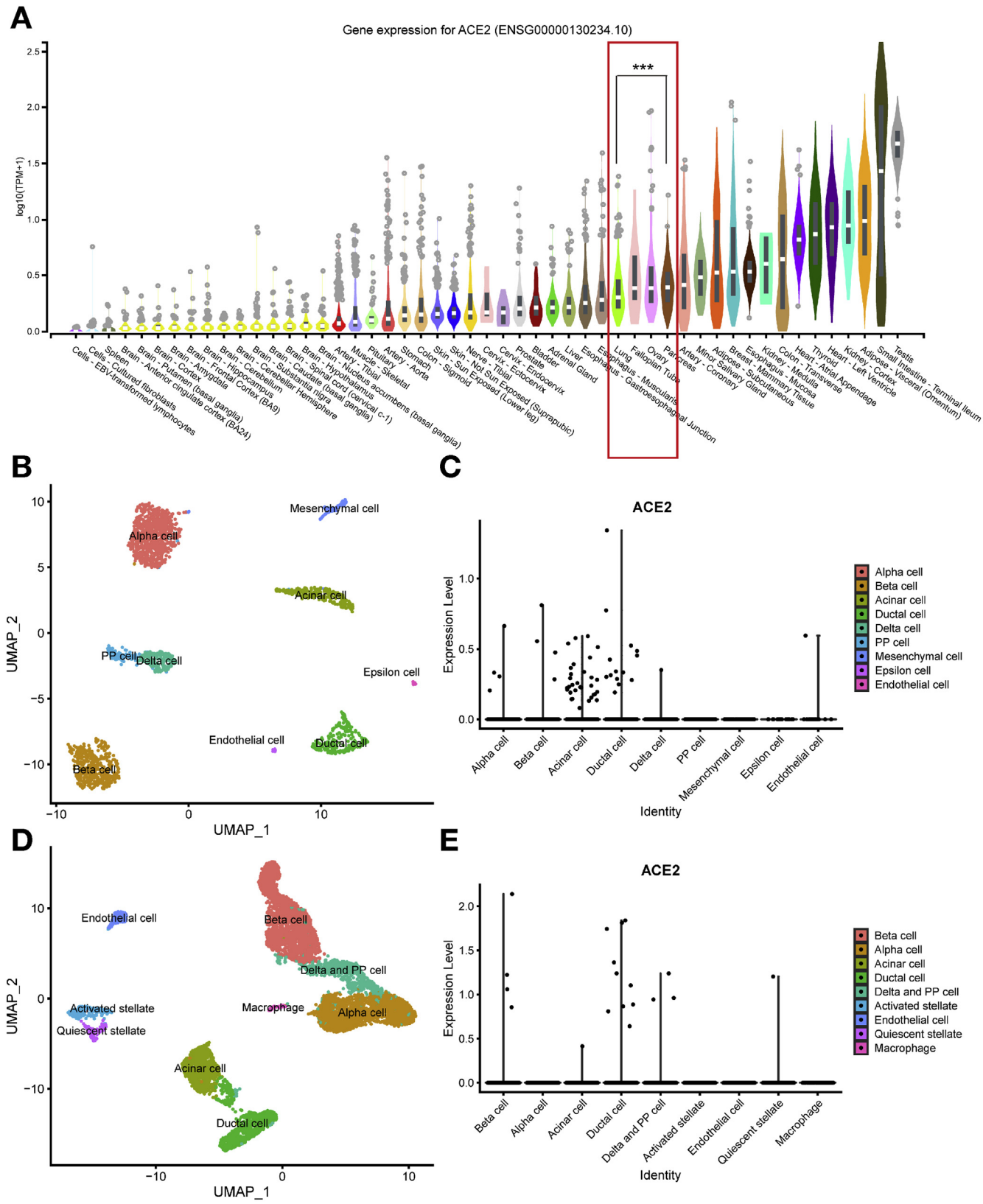

Figure 1. The expression and distribution of ACE2 in pancreas. (*A*) The messenger RNA level of ACE2 in multiple organs from GTEx samples. (*B* and *D*) The visualization of pancreatic cell distribution in GSE85241 and GSE84133. (*C* and *E*) The expression of ACE2 in different pancreatic cell in GSE85241 and GSE84133. ***$P < .001$. UMAP, uniform manifold approximation and projection.

Table 1. Summary of the Study Patients

Characteristics	All patients (n = 121)	Nonsevere (n = 54)	Severe (n = 67)
Age, *y* (range, IQR)	57 (range, 18–87; IQR, 43–72)	53 (range, 18–83; IQR, 39–67)	62 (range, 24–87; IQR, 51–73)
Sex, n (%)			
Female	46 (38.02%)	21 (38.89%)	25 (37.31%)
Male	75 (61.98%)	33 (61.11%)	42 (62.69%)
AMS/LPS increased, n (%)	13 (10.74%)	1 (1.85%)	12 (17.91%)
AMS increased	13 (10.74%)	1 (1.85%)	12 (17.91%)
LPS increased	12 (9.92%)	1 (1.85%)	11 (16.41%)
Imaging alteration, N* (%)			
Normal	8 (3.62%)	1 (1.85%)	7 (10.44%)
Enlargement or dilation	5 (4.13%)	0	5 (7.46%)
Necrosis	0	0	0

NOTE. Data are shown as the median (range, IQR), n (%), or N* (%), where N is the number of patients with increased amylase and lipase levels.
AMS, amylase; IQR, interquartile range; LPS, lipase.

pancreatic injury. Furthermore, single-cell RNA sequencing data indicated that ACE2 was expressed in both exocrine glands and islets of the pancreas.

In our study cohort, approximately 1% to 2% of nonsevere and 17% of severe patients with COVID-19 had pancreatic injury. In addition, it should be noted that some critically ill patients already had developed pancreatic injury before admission, and the possibility of drug-induced pancreatitis should be considered because of the history of taking nonsteroidal anti-inflammatory drugs and glucocorticoids in some patients. However, we should pay attention to the possibility of damage caused by SARS-CoV-2 based on the analysis of the expression of ACE2 in the pancreas and the high proportion of COVID-19 patients with pancreatic injury. Although these patients did not show signs of necrotizing pancreatitis, the consequences of pancreatic injury can be potentially serious, such as aggravating systemic inflammation, accelerating the occurrence of acute respiratory distress syndrome,[3] and even developing into chronic pancreatitis, which may have a serious impact on the health and quality of life of patients. Yang et al[4,5] reported that patients infected with SARS-CoV suffered from hyperglycemia, which might be caused by SARS-CoV damaging the pancreatic islets through ACE2. Our results show that increased attention should be paid to the pancreas in patients with SARS-CoV-2 infection, especially in severe cases.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.04.040.

References

1. Xu B, Kraemer M. Open access epidemiological data from the COVID-19 outbreak. Lancet Infect Dis 2020. https://doi.org/10.1016/S1473-3099(20)30119-5.
2. Badalov N, Baradarian R, Iswara K, et al. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol 2007;5:648–661.
3. Zhou MT, Chen CS, Chen BC, et al. Acute lung injury and ARDS in acute pancreatitis: mechanisms and potential intervention. World J Gastroenterol 2010;16:2094–2099.
4. Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23(6):623–628.
5. Yang JK, Lin SS, Ji XJ, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47:193–199.

Reprint requests
Address requests for reprints to: Zhanguo Zhang, MD, Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, 430030 Wuhan, China. e-mail: zhanguo_tjh@hust.edu.cn; fax: (86) 27-83662851.

Conflicts of interest
The authors disclose no conflicts.

Funding
This study was funded by the State Key Project on Infection Disease of China (2018ZX10723204-003).

Supplementary Methods

Analysis of Public Data Sets

We collected bulk RNA sequencing data from GTEx, which contains normal tissue and organ sequencing data from multiple individuals. The data analysis was performed online. In addition, we collected data from single-cell RNA sequencing of the pancreas NCBI-GEO (GSE85241 [4 donors with 2126 pancreatic cells], and GSE84133 [4 donors with 8569 pancreatic cells]). The details of the donors are available in a previous report.[1,2] The single-cell RNA sequencing data process is as follows: unique molecular identified expression count matrix was obtained from the database, and a Seurat object (version 3.1.4; Seurat R package) was created. Further quality control was performed, cells with high mitochondrial gene expression greater than 5% were filtered. The data were normalized and log-transformed with the LogNormalize method in the NormalizeData function. Before we performed linear dimensional reduction, the data were scaling. Then principal component analysis was performed on the data and determined the dimensionality. Finally, after clustering cells based on a graph-based clustering approach, the nonlinear dimensional reduction based on uniform manifold approximation and projection was performed on the data to analyze and visualize the data. All of the single-cell RNA sequencing data analysis was based on the Seurat R package with the default parameters.[3] The annotation of cell types was completed based on the featured genes of each cluster and the cell markers of each type of pancreas cell from CellMarker database[4] and as previously reported.[1,2]

More Details of Clinical Data

The criteria for the diagnosis and severity of the patients were followed by the diagnosis and treatment guideline for COVID-19 (trial version 6) issued by the National Health Commission of the People's Republic of China. Clinical information included age, sex, amylase and lipase levels in serum, and the imaging results including bedside ultrasound and abdominal computed tomography.

Patients with mild COVID-19 with serum amylase and lipase levels in the normal range did not undergo an imaging evaluation of the pancreas, and their pancreas was assumed to be normal. A bedside ultrasound of the abdomen was performed in all critically ill patients, and computed tomography was added if there were any abnormalities.

Supplementary Table 1. The Distribution of ACE2 in Several Types of Pancreatic Cells in 2 Single-Cell RNA Sequencing Data Sets

	GSE85241 (N = 55)	GSE84133 (N = 19)
Exocrine gland		
Duct cell	14 (25.45%)	10 (52.6%)
Acinar cell	31 (56.36%)	1 (5.26%)
Endothelial cell	1 (1.82%)	0
Pancreatic islet		
α cell	4 (7.27%)	0
β cell	4 (7.27%)	4 (21.05%)
PP and delta cell	1 (1.82%)	3 (15.79%)

NOTE. Individual differences between donors from different sources may lead to differences in the results from the 2 single-cell RNA sequencing data sets. ACE2, angiotensin-converting enzyme 2; PP, pancreatic polypeptide.

References

1. Muraro MJ, Dharmadhikari G, Grun D, et al. A single-cell transcriptome atlas of the human pancreas. Cell Syst 2016; 3:385–394.
2. Baron M, Veres A, Wolock SL, et al. A single-cell transcriptomic map of the human and mouse pancreas reveals inter- and intra-cell population structure. Cell Syst 2016; 3:346–360.
3. Stuart T, Butler A, Hoffman P, et al. Comprehensive integration of single-cell data. Cell 2019;177:1888–1902.
4. Zhang X, Lan Y, Xu J, et al. CellMarker: a manually curated resource of cell markers in human and mouse. Nucleic Acids Res 2019;47:D721–D728.

Supplementary Table 2. Clinical Characteristics of COVID-19 Patients With Pancreatic Injury

Variable, n (%) or median (IQR)	Normal range	Nonsevere (n = 1)	Severe (n = 12)
Age, *y*	–	44	62 (53–69)
Male	–	N	6 (50.0%)
BMI	20–25	28.4	27.2 (24.5–28.7)
Incubation period, *d*	2–7	4	4 (3–7)
Comorbidities			
Hypertension	–	N	5 (41.7%)
Diabetes	–	Y	5 (41.7%)
CHD	–	N	1 (8.3%)
Presenting symptoms			
Fever	–	Y	7 (58.3%)
Short of breath	–	N	8 (66.7%)
Cough	–	N	4 (33.3%)
Fatigue	–	N	4 (33.3%)
Diarrhea	–	N	2 (16.7%)
Headache	–	N	2 (16.7%)
Complications			
ARDS	–	N	6 (50.0%)
Cardiac injury	–	N	2 (16.7%)
Kidney injury	–	N	4 (33.3%)
Liver injury	–	Y	7 (58.3%)
Shock	–	N	4 (33.3%)
NSAIDs used	–	N	2 (16.7%)
Laboratory findings on admission			
WBC, $\times 10^9/L$	3.5–9.5	5.62	4.56 (3.80–10.20)
Lymphocyte count, $\times 10^9/L$	1.10–3.20	0.89	0.66 (0.43–0.92)
Neutrophil count , $\times 10^9/L$	1.80–6.30	4.13	5.02 (2.27–7.20)
Platelet count, $\times 10^9/L$	125.0–350.0	227	156 (145–280)
Hemoglobin, *g/L*	130–175	127	125 (121–150)
ALT, *U/L*	7.0–40.0	45	31 (20–78)
AST, *U/L*	13.0–35.0	37	34 (31–51)
T-BIL, $\mu mol/L$	0–21.0	10.9	11.4 (9.8–14.4)
Albumin, *g/L*	40.0–55.0	48.5	36.0 (32.5–40.0)
Creatinine, $\mu mol/L$	41.0–73.0	38	56 (42–69)
BUN, *mmol/L*	2.6–7.5	3.2	6.0 (4.4–7.2)
Amylase, *U/L*	35–135	76	62 (59–121)
>135 U/L	–	N	3 (25.0%)
Lipase, *U/L*	8–78	56	31 (24-48)
>78 U/L	–	N	3 (25.0%)
PT, *s*	11.5–14.5	12.5	12.5 (12.0–14.0)
APTT, *s*	29.0–42.0	37.5	35.6 (34.5–39.8)
INR	0.8–1.2	1.1	1.0 (0.9–1.0)
D-dimer, *mg/L*	0–1.5	0.2	0.1 (0.1–1.12)
PCT, *ng/mL*	0.02–0.05	0.04	0.32 (0.08–0.49)
CRP, *mg/L*	0–5.0	16	27.8 (18.8–86.0)
Ferritin, *ng/mL*	4.63–204	675	998 (701–1160)
Increased AMS/LPS after admission			
Amylase, U/L	35–135	175	213 (186–277)
>135 U/L	–	Y	12 (100%)
Lipase, U/L	8–78	102	156 (104–228)
>78 U/L	–	Y	11 (91.7%)
Treatments			
Oxygen support	–	N	12 (100%)
Mechanical ventilation	–	N	7 (58.3%)
Antiviral treatment	–	N	9 (75.0%)
Antimicrobial treatment	–	N	10 (83.3%)
Glucocorticoids	–	N	4 (33.3%)
ICU admission	–	N	6 (50.0%)
Outcome			
Discharge	–	Y	7 (58.3%)
Dead	–	-	5 (41.7%)

ALT, alanine aminotransferase; AMS, amylase; APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen, CHD, coronary heart disease; CRP, C-reactive protein, ICU, intensive care unit; INR, international standard ratio, LPS, lipase; NSAIDs, nonsteroidal anti-inflammatory drugs; PCT, procalcitonin, PT, prothrombin time; T-BIL, total bilirubin; WBC, white blood cells.